Remarks

Claims 90-101 are under examination. Reconsideration and further examination are respectfully requested.

Priority

A. The Office Action states that the Applicant is not entitled to claim priority to the non-provisional application 08/906,930 without filing a Petition for Unintentionally Delayed Claim of Priority. The Office notes that the Applicant's amendment to the specification includes a reference to the copending application as required under 37 CFR 1.78(a)(2) and (a)(5) was made after the latest of 4 months from the filing date of the present application, or 16 months from the filing date of the copending application.

According to 37 CFR 1.78 (a)(2)(ii)(C), "the time periods in this paragraph do not apply if the later-filed application is a non provisional application which entered the national stage after compliance with 35 U.S.C. 371 from an international application filed under 35 U.S.C. 363 before November 29, 2000." The present application is a national stage application from PCT application PCT/US98/16379, filed August 6, 1998, i.e. filed before November 29, 2000. Thus, the time limits recited by the Examiner do not apply to the present application, and applicants are allowed to make a priority claim without petition any time during the pendency of the present application. The Applicant respectfully requests that this objection be withdrawn.

B. The Office notes that the present application indicates a "continuation" of application 08/906,930. The Office states that the "application repeats a substantial portion of prior Application 08/906,930, but it also appears to add and claim additional subject matter not present in the prior application." In this regard, Applicants have amended the claim to priority to the non-provisional parent application in the specification to recite that the present application is a "continuation-in-part" of the priority application.

Examiner Query

Regarding the use of the term "transmembrane region," the Office correctly interprets the art to include amino acid 25 in the transmembrane domain of M2. The Applicants therefore recognize the accepted definition of the term as comprising residues 25-43.

Claim Rejections

Claim Rejections Under 35 USC § 112

The Applicant recognizes the withdrawal of all rejections under 35 U.S.C. § 112.

Claim Rejections Under 35 USC § 103

A. Claims 90, 91, and 93 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Kendal et al (U.S. Patent 5,290,686) in view of Black et al (J Gen Virol- 74: 1673-77- of record in the IDS), Spaete (U.S. Patent 5,474,914). The Office action characterizes these claims as reading on methods of producing monoclonal antibodies to the M2 protein of the

influenza virus comprising the administration to a subject a modified M2 polypeptide, wherein the transmembrane domain of the M2 protein has been deleted from the polypeptide, and a pharmaceutical carrier. The Office notes that the polypeptides may also comprise a substitution of the transmembrane region for one or more neutral or hydrophilic amino residues. The Office action maintains the rejection with respect to claims 90, 91, and 93, and extends it to new claims 95, 96, and 98. The Applicant continues to traverse the rejection on the grounds that combination of the cited art does not result in the modified M2 polypeptides of the claimed invention.

Kendal et al. teaches a method of making a vaccine to influenza A virus comprising recombinant M2 protein in a baculovirus expression system. Black et al. identified the transmembrane domain as comprising residues 25-43. Finally, Spaete demonstrated that the deletion of the transmembrane domain of CMV gH in combination with the expression of a chaperone, eg. soluble FGF receptor, resulted in increased CMV gH recombinant expression and/or secretion.

In order for a combination of references to render a claimed invention obvious, there would need to be both a motivation to combine specific teachings of said references and a reasonable expectation of success that such combined teachings would result in the claimed invention. The Office action, referring to MPEP 2144, argues that one skilled in the art need not have the same motivation as that of the applicant to combine the references of Spaete, Kendal et al. and Black et al. The Applicant does not object to this statement of the rules for properly combining references. Rather, the applicant's position is 1) that a motivation to combine the specific teachings of the art in the way the Office has combined them was lacking at the time of

the invention and 2) that said combination would not lead one of skill in this art to the practice of the claimed invention. Thus the combination does not render claims 90, 91, and 93 obvious.

In order for there to be motivation provide by Spaete to delete the transmembrane domain of M2, there must be at least a conscious recognition in the mind of a scientist that there is a connection between the CMV gH in Spaete and the M2 of influenza. Neither Black et al. nor Kendall et al. say anything about M2 to suggest that it shares any relevant characteristics with CMV gH. Thus, this recognition cannot come from either of these references. Nor is the necessary conscious recognition of this connection suggested by Spaete.

Even if the teaching of Spaete were clearly applicable to M2, which the applicant does not concede, there is no teaching in Spaete that the removal of a viral protein's TM domain is a key factor affecting recombinant expression. The Spaete reference teaches escort-facilitated expression of modified CMV gH and extends this method as applicable to other viral glycoproteins. It does not, however, either implicitly or explicitly, suggest that the removal of the transmembrane domain alone would effect protein expression. Spaete taught that a truncated CMV gH in combination with the expression of a chaperone, eg. soluble FGF receptor, would increase CMV gH expression. Spaete states:

> The present invention is based on the discovery of particular escorts capable of shuttling proteins coexpressed therewith to the cell surface where the expressed products can be secreted...The present invention will find use with a wide variety of proteins. Indeed, almost any desired protein can be produced using a compatible escort. (column 8, line 43)

There is no teaching in Spaete that the removal of a viral protein's transmembrane domain by itself is sufficient to affect recombinant expression. While Spaete indicates a preference for CMV gH with truncated TM domains as a "particularly preferred class of CMV

gH polypeptides" (column 5, line 54), the context of this deletion consistently involves co-expression with a chaperone protein. It is the chaperone protein that Spaete is evaluating and to which it attributes the alterations in expression and/or secretion. Thus, the results with CMV gH shown in Spaete are not clearly attributable to the deletion of the TM domain. Evidence was actually provided to the contrary, that TM deletion did not affect recombinant expression. In the context of a truncated gH gene that didn't include the TM coding sequence, Spaete says:

> A third plasmid, pCMAdgH6 (FIG. 2, ATCC Accession No. 69035), bearing a truncated gH gene as above, ...was used to transfect Chinese hamster ovary (CHO) cell line 171 ... Media from transfected cells was analyzed by a standard ELISA to screen for positive clones. RIP analysis of medium conditioned by growth of cell line 171 was not positive for truncated gH. (emphasis added) (column 26, line 6)

While Spaete teaches improved expression of modified CMVgh coexpressed with a chaperone protein, eg. FGF receptor or UL115, a similar increase in expression is not taught when the TM domain is deleted absent a chaperone protein. In the absence of such a teaching, there would be no motivation to delete the TM domain of any proteins in a context in which the chaperone proteins taught by Spaete are not being used. Thus, the skilled person would not be motivated to apply its teaching to M2.

There is also no reasonable expectation of success provided by the combined art. The Office states that the Spaete reference, in combination with the structural information of M2 provided in Black et al., identifying the transmembrane domain as comprising residues 25-43, renders obvious the applicant's deletion of these amino acids in a recombinant M2 expression vector. However, it is only the combination of escort protein and transmembrane deletion that is taught by Spaete. Based on the teaching of Spaete, it is primarily the use of chaperone protein

that provides a reasonable expectation of improved expression. The applicant does not claim the use of a chaperone. Thus, one skilled in the art would not have a reasonable expectation of success in increasing recombinant expression of M2 by simply deleting the transmembrane domain as applicant claims. In the absence of such an expectation, these claims should not be considered obvious. Withdrawal of this rejection is, therefore, respectfully requested.

B. Claims 90-93 are rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Kendal et al. in view of Black et al. and Spaete as applied to claim 90 above, and further in view of Anderson et al. (U.S. Patent 6,180,343). The Office notes that claim 92 further limits the M2 polypeptide described above to embodiments wherein "all of the deleted amino acids are replaced with from one to six glycine amino acid residues." Anderson et al. teaches that the preferred linkers for fusion proteins include gylcine polymers and glycine-serine polymers. The Office states that it would be obvious to those in the art that the linkers provided by Anderson et al. would be useful to connect two parts of the protein with the deleted transmembrane domain region.

It is the Applicant's position that the deletion of the TM domain region is non-obvious for the reasons established above. The further replacement of these deleted amino acids with glycine residues is therefore also not rendered obvious. Anderson et al. does not provide any motivation with regard to modification of M2, or particularly with regard to the deletion of the TM domain. Therefore, it does not cure the lack of teaching in Kendal et al., Black et al. and Spaete to apply the teaching of Spaete et al to M2. Furthermore, as stated above, there is no

expectation provided by said combination that the present invention (lacking a chaperone) would result in success. The Applicant therefore traverses the rejection for the reasons indicated in Section A. Thus, withdrawal of this rejection is respectfully requested.

C. Claim 94 is rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Kendal et al. in view of Black et al., Spaete and Anderson et al. as applied to claims 90, 91, and 93 above, and further in view of Ito et al. (J Virol 65:5491-98- of record in the IDS). Office notes that claim 94 further limits the method of claim 93 to embodiments wherein the M2 polypeptide is derived from the native M2 protein of the influenza virus strain A/Aichi/2/68 (H3N2) and that Ito et al. teaches the sequence of the M2 protein of the identified strain.

For the reasons established above, the deletion of the TM domain region is non-obvious. The Applicant therefore traverses the rejection for the reasons indicated in Section A. Ito et al. does not provide any motivation with regard to modification of M2. The disclosure of the sequence of M2 by Ito does not remedy the failure of the other cited art to motivate the skilled person to modify M2 as described. Therefore, it does not cure the lack of motivation in the combination of Kendal et al. in view of Black et al. and Spaete. Thus, withdrawal of this rejection is respectfully requested.

D. Claims 95, 97, and 99 are rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Kendal et al. in view of Black et al. and Spaete as applied to claims 90, 91,

and 93 above, and further in view of Kaplakis-Deliyannis et al. (Electrophoresis 14:926-936) and Spepushikin et al. (Vaccine 13:1399-1402 – of record in the April 2000 IDS).

Kaplakis-Deliyannis et al. teaches the value of using synthetic peptides for the generation of site-specific antibodies. Specifically taught is the ability of antibodies raised against the C-terminal residues 83-97 of the M2 protein to react with proteins from cells infected with influenza virus. The examiner argues that this reference provides motivation for those in the art to produce and isolate anti-influenza M2 antibodies.

Slepushikin et al. demonstrates the ability of sera from M2 vaccinated mice to react with a series of overlapping synthetic peptides spanning the entire length of the M2 protein. However, these peptides were not used as immunogens but as a means for testing the immunoreactivity of serum antibodies generated to native M2. Slepushikin et al. teaches that the sera reacted most with the N-terminal and C-terminal amino acids, identifying 3 epitopes for the animal sera. The examiner argues that this reference makes obvious to those in the art to make an M2 protein that includes the N-terminal and C-terminal sequences and that "it is not necessary that the at least 12 residues to the C-terminal end of the protein be present for the production of antibodies, as this region does not appear to be the target of the most abundant M2 antibodies." Slepushkin et al. does identify the regions of antigenicity in mice, but has no teaching at all that is relevant to the efficacy of using anything other than native protein for immunization. More importantly, not provided was any reason (i.e., motivation) for using a polypeptide that includes the N-terminal and C-terminal epitopes, but lacks the transmembrane domain.

As shown above, the Spaete reference is not correctly applied in that there was no reasonable expectation that the deletion of a viral glycoprotein's transmembrane domain, by itself, would be sufficient to increase protein expression or decrease toxicity. In the absence of such expectation, there is no motivation based on cited references to attempt TM deletion or modification in M2. There may be an expectation of maintained antigenicity based on Slepushikin et al. and Kaplakis-Deliyannis et al., however, neither of these references implicitly or explicity suggest any benefit or motivation for the removal of just the transmembrane domain or the adjacent C-terminal 12 residues. Evidence in the prior art that something can be done is not enough to make that thing obvious to try unless there is also a suggested benefit in the prior art. The burden of providing this suggestion has not been met by the cited combination of references. Thus, withdrawal of this rejection is respectfully requested.

In summary, the Office argues that the cited references can be combined to produce the claimed invention. Kendal et al. teaches a method of making a vaccine to influenza A virus comprising recombinant M2 protein in a baculovirus expression system. Black et al. identified the transmembrane domain as comprising residues 25-43. Anderson et al. teaches that the preferred linkers for fusion proteins include gylcine polymers and glycine-serine polymers. Ito et al. teaches the sequence of the M2 protein of the identified strain. Slepushikin et al. and Kaplakis-Deliyannis et al. at most provide an expectation of maintained antigenicity. However, a motivation to delete the transmembrane domain and an expectation of success in affecting recombinant expression as claimed by the Applicants is required in order for the combined

references to render obvious the claimed invention. The Office posited that Spaete fulfilled this obligation. Spaete demonstrated only that the deletion of the transmembrane domain of CMV gH, in combination with the expression of a chaperone, resulted in increased CMV gH recombinant expression. As the Applicant's method does not recite a chaperone, the Office has not satisfied the burden to provide a motivation or expectation of success in the cited art to practice the claimed invention.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending claims are believed to be warranted, and such action is respectfully requested. The Examiner is invited to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issuance.

A Credit Card Payment Form PTO-2038 authorizing payment representing $110.00 for the fee under 37 C.F.R. § 1.136 is enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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Gwendolyn D. Spratt — 8-17-04

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